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(54) Title: TRANSDERMAL DRUG DELIVERY DEVICES

(57) Abstract: Systems and devices for the transdermal delivery of the compound (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3(3-methoxyphenyl)-2-propynyl]oxime are disclosed. These devices include a drug in adhesive reservoir layer and a skin contacting adhesive layer in which the skin contacting adhesive layer acts as a rate controlling membrane. These devices also include a drug in adhesive reservoir layer and a skin contacting adhesive, where a membrane is placed between the two adhesive layers. The compound is a muscarinic agonist, useful in the treatment of a variety of cognitive disorders, including Alzheimer's Disease.

TRANSDERMAL DRUG DELIVERY DEVICES

Field of the Invention

This invention provides drug in adhesive systems for the transdermal delivery of (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3(3-methoxyphenyl)-2-propynyl]oxime, and transdermal drug delivery devices containing one or more of these systems.

Background of the Invention

The compound (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3(3-methoxyphenyl)-2-propynyl]oxime is a muscarinic agonist, which property provides it with a number of therapeutic qualities. For example the compound is useful as an analgesic agent, as a sleep aid, and in the treatment of the symptoms of senile dementia, Alzheimer's disease, Huntington's chorea, tardive dyskinesia, hyperkinesia, mania or other conditions that are characterized by decreased cerebral acetylcholine production or release. This compound, and other compounds of its class, are described in detail in U.S. Patent No. 5,306,718 to Lauffer et al.

Transdermal drug delivery devices are designed to deliver drug through the skin of a patient, providing relatively constant drug delivery over an extended period of time. There are a number of possible designs for the devices, including reservoir devices, where the drug is typically present in a liquid reservoir and delivery of the drug is controlled by a rate-controlling membrane and drug in adhesive devices, where the drug is present in a generally solid matrix that comprises a pressure sensitive skin adhesive. Depending on the permeability of the skin to the drug, other components such as skin penetration enhancers can be added to the matrix. If, however, the skin is highly permeable to the drug, steps must be taken to control diffusion of the drug through the skin in order to provide stable, extended delivery of the drug.

Summary of the Invention

The invention provides drug in adhesive systems for the transdermal delivery of (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime and transdermal drug delivery devices containing one or more of these systems.

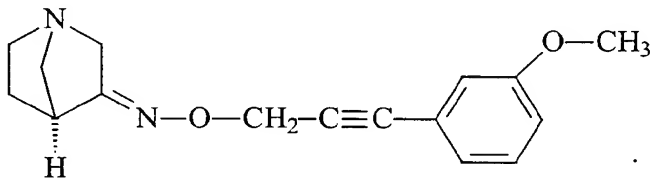
More particularly, the transdermal drug delivery devices of the invention control the rate of delivery of the drug to a subject's skin. In one aspect of the invention, the rate of delivery of the drug is controlled by a rate controlling adhesive layer that is positioned between the drug reservoir layer and the skin. In another aspect of the invention the rate of delivery of the drug is controlled by a rate controlling membrane that is positioned between the drug reservoir layer and the skin contacting adhesive layer.

The invention additionally provides a method of treating a condition characterized by decreased cerebral acetylcholine production or release in a subject comprising applying a transdermal drug device of the invention to the skin of a subject and allowing the device to remain in contact with the skin for a time sufficient to deliver a therapeutically effective amount of (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime to the subject.

Detailed Description of the Invention

The Drug

The compound (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime (referred to herein as the "drug" or the "compound") is a selective m1/m4 muscarinic agonist, useful in the treatment of a variety of conditions that are characterized by decreased cerebral acetylcholine production or release. Such conditions include senile dementia, Alzheimer's disease, Huntington's chorea, tardive dyskinesia, hyperkinesia, mania, and the like. The compound is also useful as an analgesic and sleep aid. The structure of the compound is as follows:



The compound exists in a number of isomeric forms, including stereoisomers and geometric isomers. The compound can exist in two possible geometric forms known as E-oxime and Z-oxime. The pharmacological activity resides in the Z-oxime. Therefore, the compositions of the invention contain a sufficient amount of the Z-oxime to provide the desired therapeutic effect. The invention is inclusive of compositions that contain the drug in any of its therapeutically effective stereochemical forms or isomers. The structure,

chemistry, synthesis and isomeric properties of the drug are described in detail in U.S. Patent Nos. 5,306,718 (Lauffer et. al.); 5,346,911 (Augelli-Szafran et. al.); 5,514,812 (Bucsh et. al.); and 5,534,522 (Ando et. al.), all of which are incorporated by reference herein.

The compound can be used in the devices of the invention in its free base form or in the form of a pharmaceutically acceptable salt. Examples of such salts include hydrochloric, sulfuric, phosphoric, acetic, benzoic, citric, malonic, salicylic, malic, fumaric, oxalic, succinic, tartaric, lactic, gluconic, ascorbic, maleic, aspartic, benzenesulfonic, methane- and ethanesulfonic, and hydroxymethane- and hydroxyethanesulfonic acid salts of the compound (see, e.g., J. Pharm. Sci. 66(1), pp.1-19 (1977)). In general, it is preferred to select a form of the compound that resists isomerization from the active Z-form to the inactive E-form when combined with one of the adhesive polymers described below. The free base form of the compound is preferred primarily due to its relatively slow conversion rate in the adhesive polymers used in the devices of the invention.

The Adhesives

Pressure sensitive adhesives are used in the devices of the invention in a number of contexts. The drug reservoir layer of the devices is comprised of a mixture of the drug in a pressure sensitive adhesive, and the device is adhered to the subject's skin by a layer of pressure sensitive adhesive. In some devices of the invention an adhesive layer is used to control the rate of drug delivery as well as to adhere the device to the subject's skin.

The adhesive polymer(s) utilized in the devices of the invention should be substantially chemically inert to (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime (e.g., it should not react with or degrade the compound, and preferably should not cause or accelerate conversion of the Z isomer to the E isomer), and is preferably a pressure sensitive skin adhesive. Chemical stability may be measured by preparing devices of the invention, storing them under conditions of 25°C and 60% relative humidity, and testing the devices for concentration of (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime at predetermined storage times. It is preferred that the amount of drug is more than about 95%, preferably more than about 97%, by weight of the initial amount of drug in the

device when stored at 25°C and 60% relative humidity for a period of time of 6 months. It is more preferred that the amount of drug is more than about 95%, preferably more than about 97%, by weight of the initial amount of drug in the device when stored at 25°C and 60% relative humidity for a period of time of 1 year.

Accelerated chemical stability may be measured by preparing devices of the invention, storing them under conditions of 40°C and 75% relative humidity, and testing the devices for concentration of (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime at predetermined storage times. It is preferred that the amount of drug is more than about 95%, preferably more than about 97%, by weight of the initial amount of drug in the device when stored at 40°C and 75% relative humidity for a period of time of 3 months, and more than about 90%, preferably more than about 93%, by weight of the initial amount of drug in the device when stored for a period of time of 6 months.

Examples of suitable types of adhesives include acrylates, natural rubbers, synthetic rubbers such as polyisobutylenes, polysiloxanes, polyurethanes, and other pressure sensitive skin adhesives known in the art. The adhesive polymers can be present alone or in combination.

Acrylate copolymers are preferred pressure sensitive adhesives for use in the devices of the invention. Suitable acrylate copolymers for use in an adhesive layer preferably comprise about 45 to about 95 percent by weight, more preferably 55 to 95 percent by weight, based on the total weight of all monomers in the copolymer, of one or more A monomers selected from the group consisting of alkyl acrylates containing 4 to 10 carbon atoms in the alkyl group and alkyl methacrylates containing 4 to 10 carbon atoms in the alkyl group. Examples of suitable alkyl acrylates and methacrylates include n-butyl, n-pentyl, n-hexyl, isoheptyl, n-nonyl, n-decyl, isohexyl, 2-ethyloctyl, isooctyl and 2-ethylhexyl acrylates and methacrylates. Preferred alkyl acrylates include isooctyl acrylate, 2-ethylhexyl acrylate, n-butyl acrylate, and cyclohexyl acrylate. Isooctyl acrylate is a particularly preferred A monomer.

The acrylate copolymer further comprises about 5 to about 55 percent by weight, more preferably about 5 to about 40 percent by weight, based on the total weight of all monomers in the copolymer, of one or more B monomers. Suitable B monomers include those containing a functional group selected from the group consisting of carboxylic acid,

sulfonamide, urea, carbamate, carboxamide, hydroxy, amino, oxy, oxo, and cyano. Exemplary B monomers include acrylic acid, methacrylic acid, maleic acid, a hydroxyalkyl acrylate containing 2 to 4 carbon atoms in the hydroxyalkyl group, a hydroxyalkyl methacrylate containing 2 to 4 carbon atoms in the hydroxyalkyl group, acrylamide, methacrylamide, an alkyl substituted acrylamide containing 1 to 8 carbon atoms in the alkyl group, N-vinyl-N-methyl acetamide, N-vinyl valerolactam, N-vinyl caprolactam, N-vinyl-2-pyrrolidone, glycidyl methacrylate, vinyl acetate, alkoxyethyl acrylate containing 1 to 4 carbon atoms in the alkoxy group, alkoxyethyl methacrylate containing 1 to 4 carbon atoms in the alkoxy group, 2-ethoxyethoxyethyl acrylate, furfuryl acrylate, furfuryl methacrylate, tetrahydrofurfuryl acrylate, tetrahydrofurfuryl methacrylate, propylene glycol monomethacrylate, propylene oxide methyl ether acrylate, di(lower)alkylamino ethyl acrylate, di(lower)alkylamino ethyl methacrylate, di(lower alkyl)aminopropyl methacrylamide, acrylonitrile, and methacrylonitrile. Preferred B monomers include acrylic acid, methacrylic acid, acrylamide, methacrylamide, and vinyl acetate.

The copolymer may optionally further comprise a substantially linear macromonomer copolymerizable with the A and B monomers and having a weight average molecular weight in the range of about 500 to about 500,000, preferably about 2,000 to about 100,000 and more preferably about 5,000 to about 30,000. The macromonomer, when used, is generally present in an amount of not more than about 20%, preferably not more than about 10% by weight based on the total weight of all monomers in the copolymer. Suitable macromonomers include polymethylmethacrylate, styrene/acrylonitrile, polyether, and polystyrene macromonomers. Examples of useful macromonomers and their preparation are described in Krampe et al., U.S. Patent No. 4,693,776, the disclosure of which is incorporated herein by reference.

The copolymers described above can be prepared by methods well known to those skilled in the art and described for example in U.S. Pat. No. RE 24,906 (Ulrich), U.S. Pat. No. 4,732,808 (Krampe et. al.), and International Publication Number WO 96/08229 (Garbe et. al.), the disclosures of which are incorporated herein by reference.

The inherent viscosity of the copolymer is such as to ultimately provide a suitable pressure sensitive adhesive when used in a device of the invention. Preferably the

copolymer has an inherent viscosity in the range of about 0.2 dl/g to about 2 dl/g, more preferably about 0.5 dl/g to about 1.6 dl/g.

If desired, the adhesive layer can contain components that modify the properties of the adhesive polymer, such as plasticizers, tackifiers, and the like of types and in amounts readily determinable to those of skill in the art.

The Devices

One preferred transdermal drug delivery device of the invention uses two adhesive layers that are laminated directly to one another. The first adhesive layer, which does not contact the skin of the subject, comprises a polymer and drug and serves as a drug reservoir layer. The second adhesive layer, which does contact the skin of the subject, serves to control the rate of delivery of the drug to the subject and to adhere the device to the subject's skin. The second adhesive layer comprises a polymer that is rate controlling. Thus the presence of the second adhesive layer in the device changes the skin penetration profile of the device compared to a like device where the second adhesive layer is identical in composition to the first adhesive layer, when the profile is determined using the test method described below. This control of rate of delivery of the drug may be due to differences in the affinity of the drug for the two different adhesive layers and differences in the rate of diffusion of the drug through the two different adhesive layers. These differences in affinity and/or diffusion of the drug in the two adhesive layers, as well as the relative thickness of the adhesive layers, allows the rate of delivery of the drug to be controlled. This system is referred to as the "adhesive rate controlled system".

In a particularly preferred embodiment of the adhesive rate controlled system, the adhesives to be used in the two layers are selected so that the second adhesive layer is made of an adhesive polymer that has a lower affinity for the drug than the first adhesive layer. By "lower affinity" is meant that the drug preferentially resides in the reservoir layer, so that when the system is at equilibrium the weight percentage of drug in the reservoir layer is greater than the weight percentage of drug in the rate controlling layer. The difference in the affinity of the two polymers for the drug, as well as the relative thickness of the adhesive layers, allows the rate of delivery of the drug to be controlled.

The first adhesive layer, also known as the reservoir layer, of the adhesive rate controlled device is preferably comprised of an acrylate copolymer of the type described

above. A preferred copolymer is a terpolymer of about 60 to about 80 wt-%, preferably about 65 to about 75 wt-%, based on total monomer weight, of isooctyl acrylate, about 4 to about 15 wt-%, preferably about 5 to about 10 wt-% of acrylamide and about 15 to about 35 wt-%, preferably about 15 to about 25 wt-% of vinyl acetate, with a particularly preferred weight ratio of monomers being about 75/5/20 of isooctyl acrylate/acrylamide/vinyl acetate. Another preferred copolymer is a copolymer of about 54 to about 77 wt-%, based on total monomer weight, of isooctyl acrylate, about 18 to about 39 wt-% vinyl acetate and about 2 to about 10 wt-% of polymethylmethacrylate macromonomer (PMMA), with a particularly preferred weight ratio of about 59/38/3 isooctyl acrylate/vinyl acetate/PMMA.

The reservoir layer of the device contains sufficient drug to deliver a therapeutically effective amount of the drug to a subject over the delivery period. A therapeutically effective amount of the drug is that amount which is sufficient to alleviate the symptoms of the condition being treated. The precise amount will vary with the exact nature of the condition to be treated, the status of the patient, and other factors known to those skilled in the art, but typically the dose to be administered is 0.07 to 700 mg/day, preferably about 0.1 to about 50 mg/day, and most preferably about 1 to about 30 mg/day. To deliver this amount of drug, the reservoir layer preferably contains about 5 to about 45 wt-% drug based on the total weight of the reservoir layer. More preferably the reservoir layer contains about 20 to about 35 wt-% drug.

Devices of the invention provide a therapeutically effective dose of the compound over an extended period of time, preferably from about 1 to about 14 days, more preferably about 1 day, and most preferably about 7 days.

Devices of the invention provide a therapeutically effective blood serum level of the drug to a subject over the delivery period. A therapeutically effective blood serum level of the drug is that amount which is sufficient to alleviate the symptoms of the condition being treated. The precise amount will vary with the exact nature of the condition to be treated, the status of the patient, and other factors known to those skilled in the art, but typically the blood serum level is about 0.2 to about 100 ng/mL and preferably 20 to 60 ng/mL.

It is also preferred that the rate of transdermal drug delivery be relatively constant during the extended period of time that the devices of the invention are used to provide a

therapeutically effective dose of the compound. The rate of transdermal drug delivery, also known as the transdermal flux, is defined as the rate at which drug penetrates through the skin. In the *in vitro* skin penetration test described below, the flux may be determined by measuring the amount of drug in the receptor fluid (i.e., the amount of drug that penetrates through the skin) and dividing by the area of the skin and the amount of time allowed for the drug to penetrate the skin prior to removal and replacement of the receptor fluid. The flux for each time interval is given as the average flux over the entire time interval. When more than one time interval is included in an experiment, then a maximum and minimum flux for the time period of the entire experiment may be determined (e.g., when the time intervals are 3,6,12, and 24 hours, then flux values for the time intervals 0-3, 3-6, 6-12, and 12-24 hours are obtained). It is preferred that the ratio of the maximum flux to the minimum flux is between 1.0 and about 4.0, more preferably between 1.0 and about 2.0.

In some instances there is a period of time at the start of an application period where the transdermal flux is low, sometimes referred to as a "lag time". If short time intervals are selected at the start of a penetration experiment, then the initial values of transdermal flux may be quite low due to the lag time, which would then make a calculation of the ratio between maximum flux and minimum flux quite large. It should be understood that for purposes of determining the ratio of maximum flux to the minimum flux, the flux values during the initial 24 hours of a penetration experiment are not included in determining the minimum flux unless they have reached half of the maximum flux value. Once the flux during any time interval has reached more than half of the maximum flux value, then that value and all subsequent flux values are used in determining the minimum flux.

The second adhesive layer, also known as the rate controlling layer comprises a different polymer from the first adhesive layer, such that the second adhesive layer changes the skin penetration profile of the device compared to a like device where the second adhesive layer is identical in composition to the first adhesive layer. The polymers in the first and second adhesive may differ in, for example, types and amounts of monomers, extent of reaction, crosslinking, branching, and copolymer sequences. The polymer of the adhesive rate controlled device is preferably a polyisobutylene (PIB), as it has been found that this polymer has a lower affinity for the drug than the acrylate

copolymers described above. More preferably a mixture of low molecular weight PIB and high molecular weight PIB is used. Low molecular weight PIB typically has a viscosity average MW of about 40,000 to about 70,000; high molecular weight PIB typically has a viscosity average MW of about 900,000 to 2,000,000. The high and low molecular weight polymers are combined in a ratio of low MW/high MW of about 5/1 to about 1/1, preferably about 3/1. Mixtures of PIB and acrylic copolymers can also be used. A preferred combination comprises a mixture of one or more polyisobutylenes and a copolymer of about 75/5/20 isooctyl acrylate/acrylamide/vinyl acetate, in a ratio of about 95:5 to about 80:20 PIB:acrylate.

Another preferred transdermal drug delivery device of the invention contains at least three distinct layers. The first layer comprises an adhesive that serves as a drug reservoir. The second layer comprises a rate controlling membrane that is adhered to one surface of the first layer. The third layer comprises an adhesive that is adhered to the surface of the membrane that is opposed to the surface of the membrane in contact with the first layer. This third layer contacts the skin of the subject when the device is used. This type of device is referred to as the "membrane rate controlled device".

As in the adhesive rate controlled device, the preferred reservoir layer of the membrane rate controlled device is comprised of an acrylate copolymer in combination with the drug. A preferred copolymer is a terpolymer of about 60 to about 80 wt-%, preferably about 65 to about 75 wt-%, based on total monomer weight, of isooctyl acrylate, about 4 to about 15 wt-%, preferably about 5 to about 10 wt-% of acrylamide and about 15 to about 35 wt-%, preferably about 15 to about 25 wt-% of vinyl acetate, with a particularly preferred weight ratio of monomers being about 75/5/20 of isooctyl acrylate/acrylamide/vinyl acetate. Another preferred copolymer is a copolymer of about 54 to about 77 wt-%, based on total monomer weight, of isooctyl acrylate, about 18 to about 39 wt-% vinyl acetate and about 2 to about 10 wt-% of polymethylmethacrylate macromonomer (PMMA), with a particularly preferred weight ratio of about 59/38/3 isooctyl acrylate/vinyl acetate/PMMA. The reservoir layer typically contains about 5 to about 45 wt-% of drug based on the total weight of the reservoir layer, preferably about 20 to about 35 wt-%.

The membrane is selected such that it is rate controlling. The presence of the membrane in the device changes the skin penetration profile of the device compared to a

like device not having the membrane, when the profile is determined using the test method described below. Suitable membranes include continuous film membranes and microporous membranes. Particularly preferred membranes are continuous film membranes prepared from ethylene:vinyl acetate copolymers containing from about 2 to about 28 wt- % vinyl acetate. Most preferred membranes are continuous film membranes prepared from ethylene:vinyl acetate copolymers containing about 9 wt- % vinyl acetate. The membrane thickness will generally be from about 25 μm to about 100 μm, preferably the thickness will be about 50 μm.

Because the delivery rate of the drug is controlled by the membrane, the polymer used in the second, skin contacting, adhesive layer can be selected from a variety of adhesive polymers that have a range of affinities for the drug. The polymer used in this layer can be the same as or different than the polymer used in the reservoir layer. Preferably the polymer used in the second adhesive layer has a relatively high affinity for the drug, and more preferably is an acrylic copolymer of the type described above. A particularly preferred copolymer is a copolymer of isooctyl acrylate, acrylamide, and vinyl acetate in a monomer ratio of about 75/5/20 isooctyl acrylate/acrylamide/vinyl acetate.

The skin contacting layer can initially contain no drug, as it is expected that over time drug will diffuse from the reservoir layer into the skin contacting layer, or can contain drug in a concentration similar to that of the reservoir layer.

The properties desirable in a transdermal drug delivery device are well known to those skilled in the art. For example, it is desirable to have sufficiently little cold flow that a device of the invention is stable to flow upon storage. It is also preferred that it adheres well to the skin and releases cleanly from the skin. In order to achieve resistance to cold flow, preferred levels of skin adhesion and clean release, the amount and structure of the comonomers in the copolymer, the inherent viscosity of the copolymer, and the amount and type of any adjuvants or additives are selected such that the adhesive layers obtain the desired balance of these properties.

A transdermal drug delivery device of the invention also comprises a backing. The backing is flexible such that the device conforms to the skin. Suitable backing materials include conventional flexible backing materials used for pressure sensitive adhesive tapes, such as polyethylene, particularly low density polyethylene, linear low density polyethylene, metallocene polyethylenes, high density polyethylene, polypropylene,

polyesters such as polyethylene terephthalate, randomly oriented nylon fibers, ethylene-vinyl acetate copolymer, polyurethane, natural fibers such as rayon and the like. Backings that are layered such as polyethylene terephthalate-aluminum-polyethylene composites are also suitable. The backing should be substantially inert to the components of the adhesive layer.

Transdermal drug delivery devices of the invention may be prepared using methods of preparing multi-layered devices known in the art. For example, the adhesive layers may be coextruded onto a backing or release liner, the layers can be sequentially extruded or coated onto a backing or release liner, or the layers may be separately coated onto a backing or release liner, then the two adhesive layers can be laminated together. Suitable release liners include conventional release liners comprising a known sheet material such as a polyester web, a polyethylene web, a polystyrene web, or a polyethylene-coated paper coated with a suitable fluoropolymer or silicone based coating.

Preferably the adhesive rate controlled systems of the invention are prepared by separately preparing reservoir layers and skin contacting layers. The reservoir layer is generally prepared by combining the adhesive copolymer with the drug and appropriate organic solvent or solvents (such as, for example, methanol, ethanol, isopropanol, ethyl acetate, etc). The mixture is stirred until a homogeneous coating formulation is obtained. The reservoir coating formulation is then applied to a release liner using conventional coating methods (e.g., knife coating or extrusion die coating) at a wet thickness of about 880 μm to 2200 μm, sufficient to provide a dry reservoir layer of about 14.7 mg/cm^2 to about 37.5 mg/cm^2. The coated release liner is allowed to dry and then is laminated onto a backing. The skin contacting layer is generally prepared by combining the rate controlling adhesive(s) with an appropriate organic solvent (such as, for example, methanol, ethanol, isopropanol, ethyl acetate, heptane, hexane, etc.) and stirred until homogeneous. This formulation is then applied to a release liner using conventional coating methods (e.g., knife coating or extrusion die coating). The skin contacting adhesive layer is coated at a thickness sufficient to provide a dry skin contacting adhesive layer about 10 μm to about 40 μm thick. The coated liner is allowed to dry, then the release liner is removed from the reservoir layer and the exposed adhesive surface is laminated onto the adhesive surface of the skin contacting adhesive layer. Patches of the appropriate size may then be cut from the resulting laminate. In an alternate method of production, the adhesive copolymers may

be coated onto liner and drug added to the coated adhesive copolymer as an additional step in the process, for example, using the methods disclosed in U. S. Patent No. 5,688,523 (Garbe et. al).

Membrane rate controlled devices of the invention may be prepared by preparing a reservoir layer in the manner described above. The reservoir layer formulation may be coated onto a release liner, dried and then laminated to a backing. The wet thickness of the reservoir layer is about 880 μm to about 2200 μm. A skin contacting adhesive coating formulation is prepared in the same manner as the reservoir coating formulation, using the same adhesive polymer or a different adhesive or combination of adhesives. This formulation is then applied to a release liner using conventional coating methods (e.g., knife coating or extrusion die coating) to provide a dry thickness of about 5 μm to about 50 μm. This coated liner is allowed to dry. It is then laminated onto a membrane. The devices are assembled by removing the release liner from the reservoir layer and laminating the exposed adhesive surface of the reservoir layer onto the membrane surface of the skin contacting adhesive layer. Patches of the appropriate size may then be cut from the resulting laminate.

The following examples are provided to further illustrate the invention.

Examples

In Vitro Skin Penetration Test Method

The skin penetration data given in the examples below was obtained using the following test method. A vertical diffusion cell is used with human cadaver skin.

When a transdermal drug delivery device is evaluated, the release liner is removed from a 2.0 cm^2 patch and the patch is applied to the skin and pressed to cause uniform contact with the skin. The resulting patch/skin laminate is placed patch side up across the orifice of the lower portion of the diffusion cell. The diffusion cell is assembled and the lower portion is filled with 10 mL of warm (32°C) receptor fluid (0.1 M phosphate buffer, pH 6) so that the receptor fluid is in contact with the skin. The receptor fluid is stirred using a magnetic stirrer. The sampling port is covered except when in use.

The cell is then placed in a constant temperature (32 ± 2°C) and humidity (50 ± 10% relative humidity) chamber. The receptor fluid is stirred by means of a magnetic

stirrer throughout the experiment to assure a uniform sample and a reduced diffusion barrier on the dermal side of the skin. The entire volume of receptor fluid is withdrawn at specified time intervals and immediately replaced with fresh fluid. The withdrawn fluid is filtered through a 0.45 μm filter. The last 1-2 mL are then analyzed for (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime using high performance liquid chromatography (Column: Zorbax SB-CN, 50 X 2.1 mm ID; Mobile Phase: 87 v% phosphate buffer with triethylamine adjusted to pH 3.0, 13 v% acetonitrile; Flow rate: 2 mL/min; Detector: UV, 240 nm; Run Time: 1 minute; Injection Volume: 5 μL). The cumulative amount of (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime penetrating the skin is calculated.

Drug Content Method for Stability

Transdermal drug delivery devices (20 cm^2 patches) were sealed in pouches (BAREX™/aluminum/polyester or BAREX™/aluminum/paper laminates) and stored under one or more of the following conditions of 25°C temperature/60 % relative humidity (25°C/60 % RH), 40°C temperature/75 % relative humidity (40°C/75 % RH), room temperature (RT, about 22°C), 40°C temperature, and 50°C temperature. The patches were tested for their drug content before storage and after preset storage times. An internal standard solution was prepared by adding 1.0 g ethyl paraben to 1000 mL tetrahydrofuran (THF). The liner was removed from ten 20 cm^2 patches and the patches were placed in a 1 quart (0.95 L) jar. The backing and coating were extracted using 500 mL of the internal standard solution. The sample was allowed to shake for at least 24 hours. A dilution of the sample was then prepared by placing 5 mL of the resulting solution into a 4 ounce (118.3 mL) jar and adding 100 mL 50:50 (v:v) acetonitrile/water to the jar and shaking for about 60 minutes. An aliquot of the dilution was then placed in an autosampler vial for analysis. Analysis of the samples was performed by high performance liquid chromatography (Column: Zorbax SB-CN 5 μm particle size, 25 cm x 4.6 mm ; Mobile phase: 82:18 (v/v) pH 3 buffer/acetonitrile; Buffer is 7.7 x 10^{-4} molar triethylamine in potassium phosphate solution adjusted to pH 3.0 with phosphoric acid; Flow rate: 2.0 mL/min; Detector: UV at 240 nm; Injection volume: 5 μL; Run time: 15 minutes). Results are reported as the percentage of the amount of drug remaining to the initial amount of drug.

Preparation of Adhesives

The adhesives used in the examples that follow were prepared generally according to the methods described below.

Preparation of Isooctyl Acrylate:Acrylamide:Vinyl Acetate (75:5:20) Copolymer

A master batch was prepared by combining isooctyl acrylate (621.0 g), acrylamide (41.4 g), vinyl acetate (165.6 g), 2,2'-azobis(2,4-dimethylpentanenitrile) (1.656 g), ethyl acetate (884.5 g) and methanol (87.48 g). A portion (400 g) of the resulting solution was placed in a 1 quart (0.95 L) amber glass bottle. The bottle was purged for 2 minutes with nitrogen at a flow rate of 1 L per minute. The bottle was sealed and placed in a rotating water bath at 45°C for 24 hours to effect essentially complete polymerization. The copolymer was diluted with ethyl acetate:methanol (250 g, 90:10 v:v) to 26.05% solids.

Preparation of Isooctyl Acrylate:Vinyl Acetate:Polymethylmethacrylate Macromonomer (59:38:3) Copolymer

Vinyl acetate (80.37 g), polymethylmethacrylate macromonomer (6.345 g of ELVACITE™ 1010 available from ICI Acrylics), ethyl acetate (271.95 g) and methanol (8.41 g) were charged to a 1 quart (0.95 L) amber glass bottle and then mixed on a roller until a solution was obtained. Isooctyl acrylate (124.875 g) and 2,2'-azobis(2-methylbutyronitrile) (0.3173 g) were added to the solution. The bottle was purged for 2 minutes with nitrogen at a flow rate of 1 L per minute. The bottle was sealed and placed in a rotating water bath at 57°C for 23 hours. The copolymer was diluted with ethyl acetate (62.78 g) and methanol (1.94 g) to about 38% solids.

Preparation of Isooctyl Acrylate:Vinyl Acetate:Polymethylmethacrylate Macromonomer (55:38:7) Copolymer

Vinyl acetate (80.37 g), polymethylmethacrylate macromonomer (14.80 g of ELVACITE™ 1010 available from ICI Acrylics),and ethyl acetate (370.80 g) were charged to a 1 quart (0.95 L) amber glass bottle and then mixed on a roller until a solution was obtained. Isooctyl acrylate (116.32 g) and 2,2'-azobis(2-methylbutyronitrile) (0.3173 g) were added to the solution. The bottle was purged for 2 minutes with nitrogen at a flow

rate of 1 L per minute. The bottle was sealed and placed in a rotating water bath at 57°C for 23 hours. The resultant copolymer was 28.5% solids in ethyl acetate.

Preparation of Polyisobutylene Adhesive Solution

Low molecular weight polyisobutylene (74.99 g of OPPANOL™ B10 polyisobutylene available from BASF), high molecular weight polyisobutylene (24.96 of OPPANOL™ B100 polyisobutylene), heptane (270.0 g) and ethyl acetate (180.0g) were combined and mixed until all of the polyisobutylene was dissolved.

Preparation of "Dry Adhesive"

Dry adhesive was prepared by knife coating a solution of the acrylate adhesive copolymer onto a release liner. The adhesive coated release liner was oven dried to remove the solvent and reduce the level of residual monomers. The dried adhesive was then stripped from the release liner and stored in a container until used.

Membranes

Some of the membranes used in the examples below are commercially available (e.g., COTRAN™ 9702, COTRAN™ 9717, COTRAN™ 9726 and COTRAN™ 9728 EVA controlled caliper membranes, all available from 3M Company). Others were prepared from commercially available resins using conventional extrusion methods (e.g., thermal extrusion onto a quenching roll). Examples of suitable resins include ELVAX™ ethylene-vinyl acetate (EVA) copolymers available from DuPont. In the examples that follow, the designation "X% EVA" means a membrane prepared from an ethylene-vinyl acetate copolymer which contains X weight % vinyl acetate.

Example 1

Transdermal drug delivery devices having two distinct adhesive layers separated by a membrane were prepared as described below.

A coating formulation was prepared by combining dry adhesive (8.84 g of isooctyl acrylate/acrylamide/vinyl acetate 75/5/20), (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime (1.17 g) and solvent (30 g of ethyl

acetate/methanol 90/10 v/v) and then mixing until a uniform coating formulation was obtained.

A reservoir adhesive layer was prepared as follows. The coating formulation was knife coated at a wet thickness of 60 mil (1524 μm) onto a release liner (Daubert 164P silicone coated release liner). The resulting coated liner was allowed to dry at ambient temperature for 5 hours and then it was laminated onto a backing (SCOTCHPAK™ 1109 polyester film laminate; available from 3M Company).

A skin contacting adhesive layer was prepared as follows. The coating formulation was knife coated at a wet thickness of 10 mil (254 μm) onto a release liner (Daubert 164P silicone coated release liner). The resulting coated liner was allowed to dry at ambient temperature for at least 1 hour and then the exposed adhesive surface was laminated onto a membrane (12% EVA film, 2 mil/51 μm).

The release liner was removed from the reservoir adhesive layer and then the exposed adhesive surface was laminated onto the membrane surface of the skin contacting adhesive layer. Patches were die cut from the resulting laminate. Each patch consisted of 5 layers: a backing; a reservoir adhesive layer containing 11.7% by weight of (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime; a membrane; a skin contacting adhesive layer containing 11.7% by weight of (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime; and a release liner. Skin penetration through human cadaver skin was determined using the test method described above. The skin penetration data is shown in Table 2 below where each value is the average of 3 independent determinations.

Examples 2 –20

Using the method of Example 1, a set of transdermal drug delivery devices in which the concentration of (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime in the adhesive layers, the coating weight of the reservoir adhesive layer, and the percent of EVA in the membrane were varied was prepared. The compositions are shown in Table 1 below. In each example the adhesive used was isooctyl acrylate/acrylamide/vinyl acetate 75/5/20, the coating formulation contained 25% solids, the concentration of (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime was the same in both adhesive layers, the skin

contacting adhesive layer was coated at a wet thickness of 10 mil (254 μm), and the membrane was 2 mil (51 μm) thick. Skin penetration through human cadaver skin was determined using the test method described above. The skin penetration data is shown in Table 2 below where each value is the average of 3 independent determinations.

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Table 1

Example Number	Drug Concentration	Wet Coating Thickness	% EVA
1	11.7%	1524 μm	12
2	25%	1905 μm	19
3	20%	1524 μm	12
4	20%	2160 μm	12
5	20%	1524 μm	2
6	20%	1524 μm	12
7	20%	1524 μm	12
8	25%	1143 μm	19
9	25%	1905 μm	4.5
10	20%	1524 μm	12
11	28.4%	1524 μm	12
12	15%	1905 μm	19
13	20%	889 μm	12
14	15%	1905 μm	4.5
15	20%	1524 μm	12
16	25%	1143 μm	4.5
17	15%	1143 μm	4.5
18	15%	1143 μm	19
19	20%	1524 μm	28
20	20%	1524 μm	12

Table 2

Human Cadaver Skin Penetration

Example Number	Average Cumulative Amount Penetrated ($\mu g/cm^2$)								
	3 hr	6 hr	12 hr	24 hr	48 hr	72 hr	96 hr	120 hr	144 hr	168 hr
1	16	37	90	214	462	673	855	1035	1179	1308
2	21	50	130	343	830	1289	1696	2099	2436	2725
3	35	73	165	375	763	1086	1362	1633	1865	2081
4	28	61	151	362	732	1040	1322	1584	1818	1961
5	28	62	152	357	706	919	1056	1170	1263	1350
6	21	49	115	273	612	900	1144	1395	1611	1812
7	22	50	125	306	629	875	1137	1372	1554	1703
8	101	230	494	964	1757	2469	3079	3605	4003	4312
9	154	323	619	965	1315	1540	1721	1902	2066	2213
10	46	102	242	493	877	1191	1478	1758	2006	2226
11	123	276	594	1046	1650	2124	2570	3008	3406	3759
12	59	110	239	488	925	1310	1659	1967	2222	2422
13	47	92	196	397	736	1025	1276	1510	1718	1839
14	13	32	83	210	459	633	759	869	964	1048
15	21	51	135	339	739	1070	1354	1634	1882	2105

Table 2

Human Cadaver Skin Penetration

Example Number	Average Cumulative Amount Penetrated ($\mu g/cm^2$)								
	3 hr	6 hr	12 hr	24 hr	48 hr	72 hr	96 hr	120 hr	144 hr	168 hr
16	118	223	429	735	1074	1303	1474	1637	1788	1921
17	129	251	454	686	937	1113	1264	1399	1533	1655
18	35	83	206	466	976	1425	1788	2065	2302	2486
19	66	156	371	818	1690	2462	3074	3538	3919	4213
20	182	337	603	962	1494	1964	2390	2780	3140	3456

Example 21

A coating formulation was prepared by combining dry adhesive (13.7 g of isooctyl acrylate/acrylamide/vinyl acetate 75/5/20), (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime (1.54 g) and solvent (45 g of ethyl acetate/methanol 90/10 v/v) and then mixing until a uniform coating formulation was obtained.

A reservoir adhesive layer was prepared as follows. The coating formulation was knife coated at a wet thickness of 30 mil (762 μm) onto a release liner (SCOTCHPAK™ 9742 fluoropolymer coated release liner, available from 3M Company). The resulting coated liner was allowed to dry at ambient temperature for 60 to 90 minutes and then the exposed adhesive surfaces of two portions of the coated liner were laminated to each other. The release liner was removed from one surface and the exposed adhesive surface was laminated onto a backing (SCOTCHPAK™ 1109 polyester film laminate).

A skin contacting adhesive layer was prepared as follows. The coating formulation was knife coated at a wet thickness of 7 mil (178 μm) onto a release liner (SCOTCHPAK™ 9742 fluoropolymer coated release liner). The resulting coated liner was allowed to dry at ambient temperature for 60 to 90 minutes and then the adhesive surface was laminated onto a membrane (4.5% EVA film, 2 mil/51 μm).

The release liner was removed from the reservoir adhesive layer and then the exposed adhesive surface was laminated onto the membrane surface of the skin contacting adhesive layer. Patches were die cut from the resulting laminate. Each patch consisted of 5 layers: a backing; a reservoir adhesive layer containing 10% by weight of (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime; a membrane; a skin contacting adhesive layer containing 10% by weight of (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime; and a release liner. Skin penetration through human cadaver skin was determined using the test method described above. The skin penetration data is shown in Table 4 below where each value is the average of 3 independent determinations.

Examples 22 – 38

Using the method of Example 21, a set of transdermal drug delivery devices in which the concentration of (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime in the adhesive layers, the adhesive used, and the percent of EVA in the membrane were varied was prepared. The compositions are shown in Table 3 below. In each example the same adhesive was used in both layers, the concentration of (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime was the same in both adhesive layers, and the membrane was 2 mil (51 μm) thick. Skin penetration through human cadaver skin was determined using the test method described above. The skin penetration data is shown in Table 4 below where each value is the average of 3 independent determinations.

Table 3			
Example Number	Drug Concentration	Adhesive	% EVA
22	10%	IOA/ACM/VOAc 75/5/20	19
23	10%	IOA/ACM/VOAc 75/5/20	28
24	20%	IOA/ACM/VOAc 75/5/20	4.5
25	20%	IOA/ACM/VOAc 75/5/20	19
26	20%	IOA/ACM/VOAc 75/5/20	28
27	30%	IOA/ACM/VOAc 75/5/20	4.5
28	30%	IOA/ACM/VOAc 75/5/20	19
29	30%	IOA/ACM/VOAc 75/5/20	28
30	10%	IOA/VOAc/PMMAMac 59/38/3	4.5
31	10%	IOA/VOAc/PMMAMac 59/38/3	19
32	10%	IOA/VOAc/PMMAMac 59/38/3	28
33	20%	IOA/VOAc/PMMAMac 59/38/3	4.5
34	20%	IOA/VOAc/PMMAMac 59/38/3	19
35	20%	IOA/VOAc/PMMAMac 59/38/3	28
36	30%	IOA/VOAc/PMMAMac 59/38/3	4.5
37	30%	IOA/VOAc/PMMAMac 59/38/3	19
38	30%	IOA/VOAc/PMMAMac 59/38/3	28

IOA = isooctyl acrylate

ACM = acrylamide

VOAc = vinyl acetate

PMMAMac = polymethylmethacrylate macromonomer

Table 4

Human Cadaver Skin Penetration

Example Number	Average Cumulative Amount Penetrated ($\mu g/cm^2$)									
	3 hr	6 hr	12 hr	24 hr	48 hr	72 hr	96 hr	120 hr	144 hr	168 hr
21	5	17	54	131	245	338	417	489	564	625
22	9	30	88	216	445	660	844	1006	1146	1255
23	2	10	47	149	354	544	692	828	952	1051
24	10	28	82	203	395	548	676	797	924	1033
25	4	27	135	393	859	1302	1688	2021	2341	2591
26	3	19	94	284	658	999	1282	1510	1724	1889
27	9	32	89	283	599	831	1018	1178	1333	1462
28	4	14	70	244	619	990	1332	1629	1936	2183
29	1	8	61	234	614	991	1328	1625	1924	2164
30	3	13	50	126	228	309	376	432	492	543
31	3	20	83	222	457	653	811	943	1078	1187
32	2	9	41	117	248	358	447	520	590	647
33	6	30	120	311	562	726	858	971	1092	1199
34	4	22	91	257	579	874	1128	1341	1558	1740
35	5	28	123	345	785	1190	1523	1794	2063	2285

Table 4

Human Cadaver Skin Penetration

Example Number	Average Cumulative Amount Penetrated ($\mu g/cm^2$)								
	3 hr	6 hr	12 hr	24 hr	48 hr	72 hr	96 hr	120 hr	144 hr	168 hr
36	11	33	100	250	556	805	994	1137	1280	1399
37	1	6	27	93	273	456	612	738	872	990
38	0	4	24	90	270	472	660	817	982	1126

Example 39

A coating formulation was prepared by combining dry adhesive (5200 g of isooctyl acrylate/acrylamide/vinyl acetate 75/5/20), ethyl acetate (17.56 Kg), methanol (1.96 Kg), and (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime (1300 g) and mixing until a uniform coating formulation was obtained. The formulation was allowed to stand until all air bubbles had dissipated.

A reservoir adhesive layer was prepared as follows. The coating formulation was die coated (The pump speed and die gap were selected to provide a dry coat weight of 13 $mg/cm^2 \pm 4\%$.) onto a release liner (SCOTCHPAK™ 1022 fluoropolymer coated release liner). The resulting coated liner was oven dried at 140°F (60°C) for 2 minutes, at 190°F (88°C) for 2 minutes and at 240°F (116°C) for 2 minutes. The adhesive surface of a first section of the coated liner was laminated onto a backing (SCOTCHPAK™ 1109 polyester film laminate), the release liner was removed and the exposed adhesive surface was laminated to the adhesive surface of a second section of the coated release liner. The resulting reservoir adhesive layer had a dry coat weight of 26 $mg/cm^2 \pm 4\%$.

A skin contacting adhesive layer was prepared as follows. The coating formulation was die coated (The pump speed and die gap were selected to provide a dry coat weight of 2.5 $mg/cm^2 \pm 4\%$.) onto a release liner (SCOTCHPAK™ 1022 fluoropolymer coated release liner). The resulting coated liner was oven dried at 140°F (60°C) for 2 minutes, at 190°F (88°C) for 2 minutes and at 240°F (116°C) for 2 minutes and then the adhesive surface was laminated to a 9% EVA (2 mil/51 μm) membrane (COTRAN™ 9702 EVA controlled caliper membrane).

The release liner was removed from the reservoir adhesive layer and then the exposed adhesive surface was laminated to the membrane surface of the skin contacting adhesive layer. Patches were die cut from the resulting laminate. Each patch consisted of 5 layers: a backing; a reservoir adhesive layer containing 20% by weight of (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime; a membrane; a skin contacting adhesive layer containing 20% by weight of (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime; and a release liner. Skin penetration through human cadaver skin was determined using the test method described above. The skin penetration data is shown in Table 5 below where each value is

the average of 15 independent determinations. Drug content stability data is shown in Table 6 below.

Table 5									
Human Cadaver Skin Penetration									
Average Cumulative Amount Penetrated ($\mu g/cm^2$)									
3 hr	6 hr	12 hr	24 hr	48 hr	72 hr	96 hr	120 hr	144 hr	168 hr
26	54	125	263	516	721	908	1078	1251	1415

Table 6							
Drug Content Stability (% of initial content)							
	1 mo.	2 mo.	3 mo.	4.5 mo.	6 mo.	9 mo.	12 mo.
25°C/60%RH	100.1	98.8	99.4	99.3	97.9	98.4	97.7
40°C/75%RH	98.4	97.9	97.4	96.7	93.6	-	-

Example 40

Transdermal drug delivery devices having two distinct adhesive layers directly adhered together were prepared as described below.

A reservoir adhesive layer was prepared as follows. Dry adhesive (35.0 g of isooctyl acrylate/acrylamide/vinyl acetate 75/5/20), ethyl acetate (135.0 g), methanol (15.1 g), and (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime (15.0 g) were combined and mixed until a uniform coating formulation was obtained. The formulation was knife coated at a wet thickness of 60 mil (1524 μm) onto a release liner (SCOTCHPAK™ 1022 fluoropolymer coated release liner). The resulting coated liner was allowed to dry at ambient temperature for 3 hours and then it was laminated onto a backing (SCOTCHPAK™ 1109 polyester film laminate).

A skin contacting layer was prepared as follows. The polyisobutylene adhesive solution described above was knife coated at a wet thickness of 7 mil (178 μm) onto a release liner. The coated liner was allowed to dry at ambient temperature. The "dry" adhesive layer was approximately 0.7 mil (17.8 μm) thick.

The release liner was removed from the reservoir adhesive layer and then the exposed adhesive surface was laminated onto the adhesive surface of the skin contacting

adhesive layer. Patches were die cut from the resulting laminate. Each patch consisted of 4 layers: a backing; a reservoir adhesive layer containing 30% by weight of (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime in isooctyl acrylate/acrylamide/vinyl acetate 75/5/20 adhesive; a skin contacting layer of polyisobutylene adhesive; and a release liner. Samples were allowed to sit for at least about 12 hours to allow drug to diffuse from the reservoir layer into the skin contacting layer. Skin penetration through human cadaver skin was determined using the test method described above. The skin penetration data is shown in Table 8 below where each value is the average of 3 independent determinations.

Examples 41 – 58

Using the method of Example 40, a set of transdermal drug delivery devices in which the concentration of (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime in the reservoir layer and the dry thickness of the skin contacting layer were varied was prepared. The compositions are shown in Table 7 below. In each example, the reservoir layer adhesive was isooctyl acrylate/acrylamide/vinyl acetate 75/5/20. The reservoir layer was coated at a wet thickness of 60 mil (1524 μm). The skin contacting layer was polyisobutylene (PIB). Skin penetration through human cadaver skin was determined using the test method described above. The skin penetration data is shown in Tables 8 and 10 below where each value is the average of 3 independent determinations.

Table 7		
Example Number	Drug Concentration	PIB Thickness (mil/μm)
41	35%	0.4/10.2
42	25%	1.0/25.4
43	35%	1.0/25.4
44	23%	0.7/17.8
45	30%	0.7/17.8
46	25%	0.4/10.2
47	30%	0.7/17.8
48	30%	1.1/27.9
49	37%	0.7/17.8
50	30%	0.7/17.8
51	30%	0.7/17.8
52	20%	0.5/12.7
53	20%	1.5/38.1
54	25%	1.0/25.4
55	25%	1.0/25.4
56	25%	1.0/25.4
57	30%	0.5/12.7
58	30%	1.5/38.1

Table 8										
Human Cadaver Skin Penetration										
Example Number	Average Cumulative Amount Penetrated ($\mu g/cm^2$)									
	3 hr	6 hr	12 hr	24 hr	48 hr	72 hr	96 hr	120 hr	144 hr	168 hr
40	5	24	74	174	377	580	779	975	1164	1348
41	9	28	86	207	447	680	915	1163	1408	1658
42	4	16	46	103	213	322	427	535	644	754
43	6	22	62	134	275	412	544	682	815	949
44	2	14	48	114	261	405	550	703	850	1002
45	4	18	57	137	298	460	621	786	950	1118
46	11	36	100	217	457	686	921	1176	1417	1657
47	3	17	59	137	302	458	611	769	933	1092
48	2	9	30	98	208	317	422	535	631	745
49	1	10	43	115	258	402	550	704	858	1013
50	3	19	66	153	326	494	662	832	996	1165
51	4	19	63	143	298	449	601	752	901	1052

Examples 59 – 61

Using the general method of Example 40, a set of transdermal drug delivery devices was prepared in which the composition of the skin contacting adhesive was varied. The compositions are shown in Table 9 below. The skin contacting adhesive composition was prepared by mixing solvated isooctyl acrylate/acrylamide/vinyl acetate 75/5/20 with the polyisobutylene adhesive solution described above. The coating formulation for the skin contacting layer contained about 19% solids and was coated at a wet thickness of 8 mil (203 μm). In each example, the reservoir layer adhesive was isooctyl acrylate/acrylamide/vinyl acetate 75/5/20 and the reservoir layer contained 25% (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime. The coating formulation for the reservoir layer contained 25% solids and was coated at a wet thickness of 60 mil (1524 μm). Skin penetration through human cadaver skin was determined using the test method described above. The skin penetration data is shown in Table 10 below where each value is the average of 3 independent determinations.

Table 9

Example Number	Skin Contacting Adhesive
59	95:5 PIB:IOA/ACM/VOAc 75/5/20
60	87.5:12.5 PIB:IOA/ACM/VOAc 75/5/20
61	80:20 PIB:IOA/ACM/VOAc 75/5/20

IOA = isooctyl acrylate

ACM = acrylamide

VOAc = vinyl acetate

PIB = polyisobutylene

Table 10

Human Cadaver Skin Penetration

Example Number	Average Cumulative Amount Penetrated ($\mu g/cm^2$)								
	3 hr	6 hr	13 hr	24 hr	48 hr	72 hr	96 hr	120 hr	144 hr	168 hr
52	16	49	120	263	555	867	1177	1486	1793	2008
53	5	13	36	57	132	197	265	332	400	471
54	11	30	81	144	301	461	622	788	962	1137
55	12	31	81	144	304	463	629	789	956	1120
56	9	25	73	139	309	479	655	826	999	1171
57	13	38	112	206	457	743	1020	1323	1651	1997
58	9	24	65	113	231	337	450	554	659	764
59	10	28	78	145	322	515	707	907	1113	1315
60	13	35	93	176	421	693	963	1243	1538	1831
61	11	30	87	157	346	546	745	949	1167	1395

Example 62

A reservoir adhesive layer was prepared as follows. A coating formulation was prepared by combining dry adhesive (4200 g of isooctyl acrylate/acrylamide/vinyl acetate 75/5/20), ethyl acetate (16200 g), methanol (1800 g), and (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime (1800 g) and mixing until a uniform coating formulation was obtained. The formulation was allowed to stand until all air bubbles had dissipated. The coating formulation was die coated (The pump speed and die gap were selected to provide a dry coat weight of 13 mg/cm^2 ± 4%.) onto a release liner (SCOTCHPAK™ 1022 fluoropolymer coated release liner). The resulting coated liner was oven dried at 140°F (60°C) for 2 minutes, at 190°F (88°C) for 2 minutes and at 240°F (116°C) for 2 minutes. The adhesive surface of a first section of the coated liner was laminated onto a backing (SCOTCHPAK™ 1109 polyester film laminate), the release liner was removed and the exposed adhesive surface was laminated to the adhesive surface of a second section of the coated release liner. The resulting reservoir adhesive layer had a dry coat weight of 26 mg/cm^2 ± 4%.

A skin contacting adhesive layer was prepared as follows. A coating formulation was prepared by combining low molecular weight polyisobutylene (900 g of OPPANOL B-10), high molecular weight polyisobutylene (300 g of OPPANOL B-100) and heptane (3006 g) and mixing until a uniform coating formulation was obtained. The formulation was allowed to stand until all air bubbles had dissipated. The coating formulation was die coated (The pump speed and die gap were selected to provide a dry coat weight of 1.53 mg/cm^2 ± 4%.) onto a release liner (one side silicone coated release liner). The resulting coated liner was oven dried at 125°F (52°C) for 2 minutes, at 185°F (85°C) for 2 minutes and at 225°F (107°C) for 2 minutes.

The release liner was removed from the reservoir adhesive layer and then the exposed adhesive surface was laminated to the adhesive surface of the skin contacting adhesive layer. The silicone release liner was replaced with a fluoropolymer release liner (SCOTCHPAK™ 1022 fluoropolymer coated release liner). Patches were die cut from the resulting laminate. Each patch consisted of 4 layers: a backing; a reservoir adhesive layer containing 30% by weight of (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime and 70% by weight of adhesive (acrylate/acrylamide/vinyl acetate 75/5/20) ; a skin contacting polyisobutylene adhesive

layer; and a release liner. Samples were allowed to sit for at least about 12 hours to allow drug to diffuse from the reservoir layer into the skin contacting layer. Skin penetration through human cadaver skin was determined using the test method described above. The skin penetration data is shown in Table 11 below where each value is the average of 15 independent determinations. Drug content stability data is shown in Table 12 below.

Table 11

Human Cadaver Skin Penetration

Average Cumulative Amount Penetrated ($\mu g/cm^2$)

3 hr	6 hr	12 hr	24 hr	48 hr	72 hr	96 hr	120 hr	144 hr	168 hr
16	34	80	179	396	611	819	1019	1231	1439

Table 12

Drug Content Stability (% of initial content)

	1 mo.	2 mo.	3 mo.	4.5 mo.	6 mo.	9 mo.	12 mo.
25°C/60%RH	98.3	98.0	94.8	99.0	97.4	97.6	98.6
40°C/75%RH	98.4	97.1	95.1	95.9	92.4	-	-

Examples 63-75

Using the general method of Example 21, a set of transdermal drug delivery devices was prepared in which the coating weight of the skin contacting adhesive and the reservoir layer was varied (see table 13). In each example the same adhesive (isooctyl acrylate/acrylamide/vinyl acetate 75/5/20) was used in both layers and the concentration of (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime was 20%. In each example the membrane was 2 mil (51 μm) thick and the EVA percentage was 9%. Skin penetration through human cadaver skin was determined using the test method described above. The skin penetration data is shown in Table 14 below where each value is the average of 5 independent determinations.

Table 13

Example Number	Skin Contact Layer Coat Weight [mg/cm^2]	Reservoir Layer Coat Weight [mg/cm^2]
63	2.6	26.3
64	2.6	26.3
65	5.0	23.3
66	7.7	20.2
67	7.7	20.2
68	10.0	18.1
69	12.6	13.9
70	12.6	13.9
71	2.6	26.3
72	5.0	26.3
73	7.7	26.3
74	10.0	26.3
75	12.6	26.3

Table 14

Human Cadaver Skin Penetration

Example Number	Average Cumulative Amount Penetrated ($\mu g/cm^2$)								
	3 hr	6 hr	12 hr	24 hr	48 hr	72 hr	96 hr	120 hr	144 hr	168 hr
63	35	85	177	301	562	810	1042	1257	1445	1627
64	33	75	158	222	474	718	964	1140	1294	1446
65	32	76	177	348	554	846	1089	1301	1486	1666
66	34	85	207	404	768	1155	1414	1639	1780	1924
67	33	78	180	304	708	1069	1350	1784	1974	2153
68	50	133	297	548	1013	1372	1662	1892	2074	2255
69	35	82	192	337	915	1375	1726	2012	2236	2434
70	33	83	193	300	791	1261	1616	1900	2125	2323
71	11	47	119	191	420	648	861	1064	1245	1420
72	6	45	125	220	527	806	1043	1261	1449	1626
73	10	48	126	244	559	862	1116	1339	1531	1713
74	23	70	177	310	717	1088	1383	1631	1835	2028
75	18	87	218	425	822	1189	1497	1758	1979	2185

Example 76

A coating formulation was prepared by combining dry adhesive (18.0 g of isooctyl acrylate/acrylamide/vinyl acetate 75/5/20), (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime (2.0 g) and solvent (70 g of ethyl acetate/methanol 90/10 v/v) and then mixing until a uniform coating formulation was obtained. The coating formulation was knife coated at a wet thickness of 25 mil (635 μm) onto a release liner (Daubert 164P silicone coated release liner). The resulting coated liner was dried and laminated onto a backing (SCOTCHPAK™ 1109 polyester film laminate; available from 3M Company). Drug content stability data is shown in Table 15 below.

Table 15

Drug Content Stability (% of initial content)				
	4 wk.	2 mo.	3 mo.	6 mo.
RT	100.0	99.9	100.0	99.7
40°C	100.0	99.4	98.9	97.7
50°C	99.2	97.8	96.6	93.0

Example 77

A coating formulation was prepared by combining dry adhesive (18.0 g of isooctyl acrylate/vinyl acetate/polymethylmethacrylate macromonomer 55/38/7), (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3-(3-methoxyphenyl)-2-propynyl]oxime (2.0 g) and solvent (70 g of ethyl acetate/methanol 90/10 v/v) and then mixing until a uniform coating formulation was obtained. The coating formulation was knife coated at a wet thickness of 25 mil (635 μm) onto a release liner (Daubert 164P silicone coated release liner). The resulting coated liner was dried and laminated onto a backing (SCOTCHPAK™ 1109 polyester film laminate; available from 3M Company). Drug content stability data is shown in Table 16 below.

Table 16				
Drug Content Stability (% of initial content)				
	4 wk.	2 mo.	3 mo.	6 mo.
RT	100.0	99.8	100.0	99.6
40°C	99.5	99.0	98.4	96.6
50°C	98.6	97.1	95.9	92.9

The present invention has been described with reference to several embodiments thereof. The foregoing detailed description and examples have been provided for clarity of understanding only, and no unnecessary limitations are to be understood therefrom. It will be apparent to those skilled in the art that many changes can be made to the described embodiments without departing from the spirit and scope of the invention. Thus, the scope of the invention should not be limited to the exact details of the compositions and structures described herein, but rather by the language of the claims that follow.

WHAT IS CLAIMED IS:

1. A device for the transdermal delivery of the drug (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3(3-methoxyphenyl)-2-propynyl]oxime comprising:
   (a) a drug reservoir layer comprising a therapeutically effective amount of the drug and a first pressure sensitive adhesive and
   (b) a skin contacting layer adhered to one surface of the drug reservoir layer and comprising the drug and a second pressure sensitive adhesive.

2. The device of claim 1 wherein the first pressure sensitive adhesive comprises an acrylic copolymer comprising a copolymer of
   (a) one or more A monomers selected from the group consisting of alkyl (meth)acrylates containing 4 to 10 carbons in the alkyl group and
   (b) one or more ethylenically unsaturated B monomers containing a functional group selected from the group consisting of carboxylic acid, sulfonamide, urea, carbamate, carboxamide, hydroxy, amino, oxy, oxo and cyano.

3. The device of claim 2 wherein the A monomer(s) is selected from the group consisting of isooctyl acrylate, 2-ethylhexyl acrylate, butyl acrylate, and cyclohexyl acrylate.

4. The device of claim 2 wherein the B monomer(s) is selected from the group consisting of acrylic acid, methacrylic acid, acrylamide, vinyl acetate and methacrylamide.

5. The device of claim 2 wherein the acrylic copolymer further comprises one or more substantially linear macromonomers copolymerizable with the A and B monomers.

6. The device of claim 1 wherein the second pressure sensitive adhesive comprises a polysiloxane, an acrylate, a natural rubber, or a synthetic rubber.

7. The device of claim 6 wherein the second pressure sensitive adhesive layer comprises polyisobutylene.

8. The device of claim 1 wherein the drug is present in the reservoir layer in an amount of about 5 to about 45 wt-% based on the total weight of the reservoir layer.

9. A device for the transdermal delivery of the drug (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3(3-methoxyphenyl)-2-propynyl]oxime comprising:

(a) a drug reservoir layer comprising a therapeutically effective amount of the drug and a first pressure sensitive adhesive;

(b) a rate controlling membrane adhered to one surface of the drug reservoir layer; and

(c) a skin contacting layer adhered to the surface of the membrane that is opposed to the surface of the membrane in contact with the reservoir layer and comprising a second pressure sensitive adhesive.

10. The device of claim 9 wherein the first and second pressure sensitive adhesives independently comprise an acrylic copolymer.

11. The device of claim 9 wherein the skin contacting layer also includes drug.

12. The device of claim 10 wherein each acrylic copolymer independently comprises a copolymer of:

(a) one or more A monomers selected from the group consisting of alkyl (meth)acrylates containing 4 to 10 carbons in the alkyl group and

(b) one or more ethylenically unsaturated B monomers containing a functional group selected from the group consisting of carboxylic acid, sulfonamide, urea, carbamate, carboxamide, hydroxy, amino, oxy, oxo and cyano.

13. The device of claim 12 wherein the A monomer(s) is selected from the group consisting of isooctyl acrylate, 2-ethylhexyl acrylate, butyl acrylate, and cyclohexyl acrylate.

14. The device of claim 12 wherein each B monomer(s) is independently selected from the group consisting of acrylic acid, methacrylic acid, acrylamide, vinyl acetate and methacrylamide.

15. The device of claim 12 wherein at least one of the acrylic copolymers further comprises one or more substantially linear macromonomers copolymerizable with the A and B monomers.

16. The device of claim 9 wherein the rate controlling membrane comprises an ethylene vinyl acetate copolymer.

17. The device of claim 9 wherein the drug is present in the reservoir layer in an amount of about 5 to about 45 wt-% based on the total weight of the reservoir layer.

18. A method of treating a condition characterized by decreased cerebral acetylcholine production or release in a mammal comprising applying a device according to claim 1 to the mammal and allowing the device to remain in contact with the skin for a time sufficient to deliver a therapeutically effective amount of (R)-(Z)- 1-azabicyclo[2.2.1]heptan-3-one, O-[3(3-methoxyphenyl)-2-propynyl]oxime to the mammal.

19. The method of claim 18 wherein the condition is Alzheimer's disease.

20. A method of treating a condition characterized by decreased cerebral acetylcholine production or release in a mammal comprising applying a device according to claim 9 to the mammal and allowing the device to remain in contact with the skin for a time sufficient to deliver a therapeutically effective amount of (R)-(Z)- 1-

azabicyclo[2.2.1]heptan-3-one, O-[3(3-methoxyphenyl)-2-propynyl]oxime to the mammal.

21. The method of claim 20 wherein the condition is Alzheimer's disease.

22. A method of treating a condition characterized by decreased cerebral acetylcholine production or release in a mammal comprising delivering (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3(3-methoxyphenyl)-2-propynyl]oxime to a mammal via a transdermal drug delivery device in an amount of about 0.1 to about 50.0 mg/20 cm^2 patch/day thereby causing the serum concentration of (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3(3-methoxyphenyl)-2-propynyl]oxime in the mammal to be about 0.2 to about 100 ng/mL for a period of time from about 2 to about 14 days.

23. The method of claim 22 wherein the (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3(3-methoxyphenyl)-2-propynyl]oxime is delivered in an amount of 1.0 to 30.0 mg/20 cm^2 patch/day, the serum concentration of (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3(3-methoxyphenyl)-2-propynyl]oxime in the mammal is about 20 to about 60 ng/mL, and the period of time is about 7 days.

24. A method of treating a condition characterized by decreased cerebral acetylcholine production or release in a mammal comprising delivering (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3(3-methoxyphenyl)-2-propynyl]oxime to a mammal via a transdermal drug delivery device in an amount of about 0.1 to about 50.0 mg/20 cm^2 patch/day wherein the ratio of the maximum flux to the minimum flux is between 1.0 and about 4.0 for a period of time from about 2 to about 14 days.

25. The method of claim 24 wherein the ratio of the maximum flux to the minimum flux is between 1.0 and about 2.0.

26. A method of treating a condition characterized by decreased cerebral acetylcholine production or release in a mammal comprising delivering (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3(3-methoxyphenyl)-2-propynyl]oxime to a mammal via a transdermal drug delivery device in an amount of about 7.5 to about 50.0 mg/20 cm^2 patch/day for a period of time from about 1 to about 14 days.

27. A method of treating a condition characterized by decreased cerebral acetylcholine production or release in a mammal comprising delivering (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3(3-methoxyphenyl)-2-propynyl]oxime to a mammal via a transdermal drug delivery device in a therapeutic amount for a period of time from about 2 to about 14 days.

28. A method of treating a condition characterized by decreased cerebral acetylcholine production or release in a mammal comprising delivering (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3(3-methoxyphenyl)-2-propynyl]oxime to a mammal via a transdermal drug delivery device thereby causing the serum concentration of (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3(3-methoxyphenyl)-2-propynyl]oxime in the mammal to be about 0.2 to about 100 ng/mL for a period of time from about 1 to about 14 days.

29. The method of claim 28 wherein the serum concentration is between about 20 and about 60 ng/mL .

30. A device for the transdermal delivery of the drug (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3(3-methoxyphenyl)-2-propynyl]oxime comprising a pressure sensitive adhesive layer comprising a therapeutically effective amount of the drug wherein the amount of drug is more than about 95% by weight of the initial amount of drug in the device when stored at 25°C and 60% relative humidity for a period of time of at least 6 months.

31. The device of claim 30 wherein the period of time is 1 year.

32. A device for the transdermal delivery of the drug (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3(3-methoxyphenyl)-2-propynyl]oxime comprising a pressure sensitive adhesive layer comprising a therapeutically effective amount of the drug wherein the amount of drug is more than about 90% by weight of the initial amount of drug in the device when stored at 40°C and 75% relative humidity for a period of time of 6 months.

33. A device for the transdermal delivery of the drug (R)-(Z)-1-azabicyclo[2.2.1]heptan-3-one, O-[3(3-methoxyphenyl)-2-propynyl]oxime comprising a pressure sensitive adhesive layer comprising a therapeutically effective amount of the drug wherein the amount of drug is more than about 95% by weight of the initial amount of drug in the device when stored at 40°C and 75% relative humidity for a period of time of 3 months.